RCE/1648
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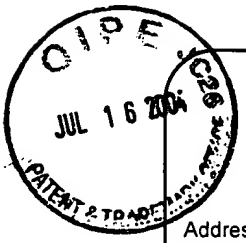
PTO/SB/30 (09-03)



Request For Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	09/905,338
Filing Date	July 13, 2001
First Named Inventor	Watkins, Michael I.
Art Unit	1648
Examiner Name	Stucker
Attorney Docket Number	02558B-059411US

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

   a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.
      i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
      ii. ☐ Other _____

   b. ☒ Enclosed
      i. ☒ Amendment/Reply
      ii. ☐ Affidavit(s)/ Declaration(s)
      iii ☒ Information Disclosure Statement (IDS)
      iv. ☐ Other _____

2. Miscellaneous

   a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

   b. ☐ Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

   a. ☒ The Director is hereby authorized to charge the following fees, or credit any overpayments, to Deposit Account No. 20-1430
      i. ☒ RCE fee required under 37 CFR 1.17(e)
      ii. ☒ Extension of time fee (37 CFR 1.136 and 1.17) Two (2) months
      iii. ☐ Other _____

   b. ☐ Check in the amount of $ _____ enclosed

   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization of PTO-2038.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Name (Print /Type)	Joel G. Ackerman	*Registration No. (Attorney/Agent)*	24,307
Signature		*Date*	July 13, 2004

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, or facsimile transmitted to the U.S. Patent and Trademark Office on the date shown below.

Name (Print /Type)	Lois M. Simón		
Signature		Date	July 13, 2004

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07/19/2004 HALI11 00000083 201430 09905338

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On **July 13, 2004**

TOWNSEND and TOWNSEND and CREW LLP

By: _____
Lois M. Simón

PATENT
Docket No.: 02558B-059411US
Client Ref. No.: BRP00091 (divisional)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Michael I. Watkins and Richard B. Edwards

Application No.: 09/905,338

Filed: July 13, 2001

For: MULTIPLEX FLOW ASSAYS PREFERABLY WITH MAGNETIC PARTICLES AS SOLID PHASE

Examiner: Stucker

Art Unit: 1648

RESPONSE - REQUEST FOR CONTINUED EXAMINATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Office Action dated February 13, 2004, Applicants respectfully request continued examination of this Application on the basis of the comments that follow.

Claims 21-23, 26, 27, 29 and 54-58 were again rejected as anticipated by Walt et al., U.S. patent 6,023,540, and as obvious over the combination of Walt et al. with the Coulter British patent 1,561,042.

Applicants again submit that the disclosure of Walt et al. is insufficient to render the present claims anticipated. For the reasons previously stated, compositions as claimed herein are not disclosed within the four corners of this reference.

Additionally, Applicants have submitted two Declarations under 37 C.F.R. 1.131. The first was submitted in order to antedate a reference having an effective date of September 25, 1997. It is the second declaration on which Applicants currently rely, which was submitted with the previous response. This declaration states that the work described in it was conducted prior to March 14, 1997, and is deemed sufficient to remove Walt et al. as prior art, whatever its disclosure may be.

Withdrawal of the rejections based on Walt et al. is respectfully requested.

All claims under examination are rejected as anticipated by JP 61-132869. However, Applicants submit that this reference does not anticipate these claims.

The independent claim in this Application, claim 21, reads as follows:

21. A composition comprising a plurality of solid-phase assay reagents selectively active in a plurality of assays each for a different analyte, each said solid-phase assay reagent comprising a binding species that is selectively active in a single assay and coupled to one of a plurality of microparticles of magnetically responsive material, the sizes of said microparticles varying in size over a range that is an aggregate of a plurality of subranges, each subrange distinguishable from other subranges of said aggregate by flow cytometry and by the binding species coupled thereto, said microparticles being suitable for use in a multiplex assay procedure that includes the use of flow cytometry.

The composition thus requires a plurality of reagents, each for a different analyte, coupled to a plurality of magnetically responsive particles of varying size subranges, with each size subrange distinguishable from the others by flow cytometry and by the coupled binding species, the microparticles being suitable for use in a multiplex assay procedure that includes the use of flow cytometry.

The examiner takes the position that the reference discloses microparticles that are of different diameter, fluorescently labeled, and optionally magnetized. However, this characterization combines statements in the reference that relate to two different embodiments of the work described therein, and which are not combinable. One relates to an assay for multiple analytes, the other to the use of magnetic particles for separation of a single type of bound and unbound analyte.

The reference overall discloses various techniques for separating bound (B) and unbound or free (F) antibodies. The first embodiment is found at the bottom of page 5 of the reference (English translation). In this embodiment mixed carriers are used, in which antigens are bound to latex particles having different particle sizes. B-F separation is then carried out, and concentrations of a plurality of analytes can be ascertained from the fluorescence intensities.

Magnetized latex particles are used in another embodiment of the process, which is described at the top of page 6. Here only a single antibody is analyzed for, and the magnetic particles are used to separate bound antibody from the free antibody by use of an electromagnet. This is a typical magnetic separation process.

The two embodiments involve different techniques and processes. While both are included under the general topic of techniques for separating bound from free antibody in this reference, they are described as alternative processes and are not intended to be used in any combination.

The combination of the two techniques is similar in nature to a rejection earlier in the prosecution of this application, namely that over the combination of Bibette et al. (which disclosed magnetic particles but not for use in multiplex assays) with the British patent of Coulter et al. (which disclosed multiplex assays that did not use magnetic particles). In response to that rejection, Applicants pointed out that the claims called for magnetic particles that were differentiated from and differentiable from, each other. That is not the case with the particles of the second embodiment of this reference.

This rejection was withdrawn based on Applicants' arguments, which are summarized immediately below.

The presently claimed particles are for use in a process that, as described in the specification, requires re-suspension of the particles after the magnetic field has been applied and the use of flow cytometry on the resuspended particles. Flow cytometry is a process that is sensitive to the composition of the particles and their interactions with each other. Adding a magnetic character to the particles can give the particles a strong interparticle attraction or repulsion (both of which can affect their ability to be resuspended). Adding a magnetically responsive component to the particle mass can seriously affect the properties of the particle. In the context of the present invention, magnetically responsive particles must do much more than simply offer a means to separate the particles from a liquid, or separate bound from free antibody, by placing a magnet nearby.

The problems and risks that arise when resuspension and flow cytometry are applied to magnetic particles in a multiplex assay system, are neither recognized nor addressed in the prior art, including JP 61-132869. Specifically:

None of the prior art on either flow cytometry or magnetized particles addresses the risk that magnetized particles will settle out before passing through the flow cytometry cell. Note that this risk is much greater with magnetic particles than it is with particles of latex, which is the traditional particle material used in flow cytometry.

None of the prior art on either flow cytometry or magnetized particles addresses the risk that magnetized particles upon resuspension will not completely separate and instead remain as aggregates that will clog the flow cell. Latex particles, such as are used in Coulter, or in the first embodiment of JP 61-132869, which have much less a tendency to form aggregates, do not present this problem, nor do they present a risk of comparable magnitude.

None of the prior art on either flow cytometry or magnetized particles addresses the risk of losing magnetic character of having magnetic characters of widely

varying magnitude that would interfere with the particles' ability to function uniformly as magnetic particles, when the particles are fabricated in different sizes or with different dyes or some other differentiation parameter.

JP 61-132869 does not provide any assistance in dealing with these potential problems. The two embodiments relied on in the Office Action involve different techniques, and information about one is not necessarily combinable with information about the other. In particular, it would not be obvious to combine the teaching of the second embodiment to use magnetic particles with that of the first embodiment, a multiplex determination that does not use, or need to use, magnetic particles.

Cited in the accompanying Information Disclosure Statement is Canadian patent application 2,072,548 and its counterpart, US patent 5,561,070. This reference discloses a multiplex process for detection and analysis of antibodies to phospholipids. The process preferably uses a plurality of polystyrene beads of varying sizes ('070 patent, col. 4 line 6), but the following sentence contains a typical catchall statement later in that paragraph that other particulate materials known in the art may be used, including magnetic beads (type unspecified).

Again, for the reasons just discussed, a substitution of magnetic beads for typical non-magnetic polymeric beads in such a process is not a simple matter; it is much easier said than done. Applicants submit therefore that the mere statement in this reference that magnetic beads can be used in the process, without more, is not an enabling disclosure.

In addition, at least some of the dependent claims contain further distinctions that are not taught in the reference.

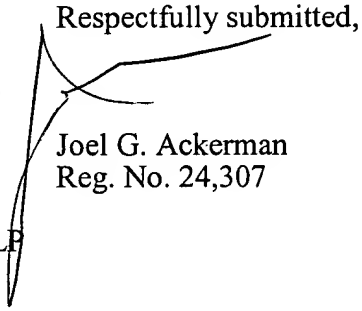
Claims 22-25 define particle properties including size and porosity that are not disclosed in the reference.

Claims 54-58 call for particles that are differentiable both by size and by a differentiation parameter other than size. Such particles likewise are not disclosed in the Japanese reference.

Applicants submit that the current claims are therefore patentable over the cited art, and request an early notice to that effect.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned.

Respectfully submitted,



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